National Institute of Allergy and Infectious Diseases
National Institutes of Health

July 9, 2002

Mother-to-Infant HIV Transmission Rate Less Than 2 Percent in Phase III Perinatal Trial

The risk of transmitting HIV from a mother to her newborn infant can be reduced to 1.5 percent in HIV-positive women who receive antiretroviral therapy and appropriate medical and obstetrical care during pregnancy, according to data published in the July 10th edition of *The Journal of the American Medical Association*. The addition of a simple two-dose regimen of nevirapine, however, did not further reduce the rate of transmission in this population. Nevirapine has previously been shown to reduce transmission of HIV by women who do not receive antiretroviral therapy during pregnancy.

The low transmission rate was observed in a randomized, controlled clinical trial conducted by the Pediatric AIDS Clinical Trials Group (PACTG). The study, known as PACTG 316, was conducted in more than 100 study sites in the United States, France, Spain, Italy, Belgium, England, Germany, Sweden, Switzerland, Bahamas, and Brazil. It was sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Child Health and Human Development (NICHD), and received additional support from the Agence Nationale de Recherches sur le SIDA (ANRS) in France. Enrollment at European sites other than France was facilitated through the European Collaborative Study, which receives funding from the European Commission and the UK Medical Research Council. Boehringer-Ingelheim, Inc., was the pharmaceutical sponsor.

In industrialized countries, many HIV-infected pregnant women take combination antiretroviral therapy for their HIV disease. PACTG 316 was designed to evaluate whether adding nevirapine (NVP) to standard regimens would have any extra benefit in reducing mother-to-infant transmission. This question was particularly important since HIVNET 012, a study conducted by NIAID-funded researchers in Uganda, showed that in a population of HIV-infected pregnant women who do not receive any antiretroviral therapy, nevirapine reduces the risk of HIV transmission by nearly 50 percent compared with a very short course of zidovudine (AZT). As a result of the lower-than-expected HIV transmission rates, the data and safety monitoring board reviewing the interim findings recommended the study stop enrollment earlier than anticipated because it was futile to try to prove that nevirapine could further reduce the transmission rate.

In PACTG 316, a placebo or a two-dose nevirapine regimen—one dose to the mother during labor and one to the child within 72 hours of delivery, the same regimen used in the Ugandan study—was provided. Women in the study also received appropriate antiretroviral therapy and prenatal care. Mothers in the study were taking AZT, AZT/3TC, or other drug combinations with and without protease inhibitors. More than half of the mothers achieved suppression of HIV RNA to less than 400 copies/milliliter (ml), and 11 percent had HIV RNA levels above 10,000 copies/ml.

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The data just published, based on 1,248 HIV-positive women and their infants, show an overall HIV transmission rate of 1.5 percent. Nine of the 631 infants (1.4 percent) who received nevirapine became HIV-infected compared with 10 of 617 infants (1.6 percent) receiving placebo. These results suggest no additional benefit to nevirapine in this group. In addition, researchers determined that 10 of the 19 infected infants (5 nevirapine recipients, 5 placebo recipients) were infected prenatally and therefore could not have benefited from the nevirapine regimen.

The researchers stress that although the addition of nevirapine to existing antiretroviral regimens did not further reduce mother-to-infant transmission of HIV in PACTG 316, nevirapine effectively reduces HIV transmission in populations with higher perinatal transmission rates, as indicated by other African studies.

The 1.5 percent transmission rate was lower than expected. Since the implementation of standard guidelines for reducing the risk of mother-to-infant transmission, studies have suggested that the rate of transmission is between 2 and 5 percent. In countries where this care is not available, transmission rates may exceed 20 percent. The low transmission rate observed in PACTG 316 underscores the importance of counseling and testing all pregnant women and the need for appropriate medical and obstetrical management of HIV infection in reducing the risk of mother-to-infant HIV transmission.

Overall, the two-dose nevirapine regimen was well tolerated by the mothers and infants. Short-term serious side effects rarely were observed in the women or infants in the study and did not differ between the nevirapine and placebo groups. However, additional data on long-term safety of antiretroviral drugs in pregnancy is still needed. Long-term follow-up is recommended for all infants exposed to antiretroviral treatments in utero or as newborns.

The development of resistance from the nevirapine regimen continues to be evaluated. This study and others reveal that some women with detectable virus and exposed to a single dose of nevirapine demonstrate resistant viral strains when tested shortly after delivery. However, based on follow-up from HIVNET 012, this resistance diminishes over time. While the initial detection of resistance appears less problematic for future use in preventing mother to infant transmission, it is of unclear significance when considering future maternal treatment options.

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